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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,838	07/13/2001	Avi Ashkenazi	10466/72	5331

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,838	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/28/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/28/2004 has been entered.

Claims 44-46, 49-51 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Priority

The present claims are directed to or encompass a polypeptide comprising the amino acid sequence of SEQ ID NO: 114. Based on the priority statement filed August 26, 2002 and an inspection of the patent applications, the examiner has concluded that the claimed subject matter is supported by the disclosure in application serial no. PCT/US00/04414, filed February 22, 2000 but is not supported by any of the others because the claimed subject matter is not supported in the manner provided by 35 U.S.C. 112, first paragraph in any of the earlier filed applications.

Applicants argue that although Pennica teaches a lack of correlation for the WISP-2 gene, Pennica does teach a correlation for the WISP-1 gene. Applicant's arguments have been fully considered but they are not persuasive. The correlation for the WISP-1 gene does not vitiate the lack of correlation for the WISP-2 gene.

Applicants argue that Pennica's teachings are specific for the WISP family of genes, that Pennica teaches nothing regarding a lack of correlation in genes in general, that the examiner has to provide evidence that it is more likely than not that a lack of correlation exist in general in order to make a prima facie case showing a lack of utility, and that based on Pennica such a teaching in general has not been made. Applicant's arguments have been fully considered but they are not persuasive. The M.P.E.P. reminds Office personnel that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. The examiner has cited Pennica (U) as countervailing evidence that that shows that one of ordinary skill in the art would have a legitimate basis to doubt the utility of the PRO317 polypeptide. The skilled artisan would not know if the expression of the PRO317 polypeptide would be upregulated, down-regulated, or unchanged in cancer. Therefore, the gene amplification data does not impute a specific, substantial, and credible utility to the PRO717 polypeptide.

The examiner also rejects Applicants' argument that the teachings of Pennica are specific to WISP genes and that Pennica has no teaching regarding correlation of gene amplification and protein expression in general. Pennica is evidence that not all gene amplifications are associated with overexpression of the corresponding gene product and that the skilled artisan would not have appreciated that PRO317 gene amplification, without more, would have suggested a specific and substantial patentable utility for the PRO317 polypeptide. The examiner is not arguing that a correlation between PRO317 gene amplification and PRO717 polypeptide expression does not exist. The examiner is

arguing that the present specification fails to disclose what that correlation is or the significance of any such correlation. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

Applicants argue that it is generally well understood in the art that DNA copy number influences gene expression, and that Orntoft, Hyman, and Pollack collectively teach that gene amplification correspondingly increases mRNA expression in general. Applicant's arguments have been fully considered but they are not persuasive. Orntoft appears to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft does not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (page 40, right column). This analysis was not done for PRO317 in the instant specification. That is, it is not clear whether or not PRO317 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft is not clear. Hyman used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman also does not support utility of the claimed proteins based on amplification of the PRO317 gene. Pollack also used CGH technology, concentrating on large chromosome regions showing high amplification

(page 12965, full paragraphs 1-2). Pollack did not investigate protein levels. Therefore, Pollack also do not support the asserted utility of the claimed invention based on amplification of the PRO317 gene. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO317 proteins have utility in the fields of cancer diagnostics and cancer therapeutics based on amplification of the PRO317 gene are not substantial.

Applicants argue that the proper legal standard is to show that it is more likely than not that a correlation exist, that the showing in the Polakis declaration greatly exceeds this legal standard, and that the skilled artisan would reasonably expect that the PRO317 polypeptide is concomitantly overexpressed. Applicant's arguments have been fully considered but they are not persuasive because the Polakis declaration is not persuasive, as discussed below.

The declaration of Dr. Polakis under 37 CFR 1.132 filed 06/28/2004 is insufficient to establish priority for the claimed invention prior to February 22, 2000 because: In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30

of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, the instant specification provides no information regarding increased mRNA levels of PRO317 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. A "dogma" is an authoritative principle, belief, or statement of ideas or opinion, especially one considered to be absolutely true. However, Haynes (U), who studied more than 80 proteins relatively homogeneous in half-life and expression level, found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1). Hancock (V) states that "the

markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" (full paragraph 2). Haynes and Hancock provide evidence that that Dr. Polakis' asserted dogma is not absolutely true.

Applicants argue that even in the absence of a correlation gene amplification and protein levels the polypeptide would still have a credible, specific and substantial utility because simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification, which leads to better determination of suitable therapy, as supported by the declaration of Dr. Ashkenazi and the teachings of Hanna and Mornin. Applicant's arguments have been fully considered but they are not persuasive because the Ashkenazi declaration is not persuasive, as discussed below.

The declaration of Dr. Ashkenazi under 37 CFR 1.132 filed 06/28/2004 is insufficient to establish priority for the claimed invention prior to February 22, 2000 because:

Declarant asserts that amplification of certain genes gives cancer cells an advantage relative to normal cells. Declarant asserts that if the mRNA and gene product are over-expressed, then the gene product is a promising candidate for therapy. Declarant's arguments have been fully considered but they are not persuasive. The present claims are directed to or encompass the PRO317 polypeptide (SEQ ID NO: 114). The specification discloses (example 92 and table 8) amplification of the PRO317 gene DNA. However, no information is provided in the gene amplification data regarding the level of expression, activity, or role in cancer of the PRO317 polypeptide.

Declarant asserts that a gene protein product of an amplified gene is useful regardless of the expression level of the protein because parallel monitoring of gene

amplification and protein expression provides better tumor diagnosis, treatment, or classification. Declarant's arguments have been fully considered but they are not persuasive. As discussed above, no information is provided in the gene amplification data regarding the level of expression, activity, or role in cancer of the PRO317 polypeptide. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Rather than setting a de minimis standard, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. The examiner accepts for argument's sake that a person skilled in the art could derive some data regarding PRO317 polypeptide expression in tumors in which the PRO317 gene is amplified. The examiner can also accept, for argument's sake, that such data could be used to correlate PRO317 polypeptide expression with PRO317 polynucleotide amplification. The skilled artisan might also be able to derive a practical way of using this data. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. In effect, Applicants' position is that the claimed PRO317 polypeptides are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form."

Applicant's arguments have been fully considered but they are not persuasive because the examiner does not agree with Applicants' interpretation of Hanna. Hanna clearly states that the clinical significance of the discordance between gene amplification and protein expression is unclear (first page, right column, last paragraph). Hanna states

that HER-2/neu testing will utilize IHC as a screen, followed by FISH in IHC-negative cases, presumably to better understand the significance of these discordant results. This teaching does not provide a specific benefit in currently available form for the presently claimed PRO317 polypeptide. Rather than setting a de minimis standard, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. The examiner accepts for argument's sake that a person skilled in the art could derive some data regarding PRO317 polypeptide expression in tumors in which the PRO317 gene is amplified. The examiner can also accept, for argument's sake, that such data could be used to correlate PRO317 polypeptide expression with PRO317 polynucleotide amplification. The skilled artisan might also be able to derive a practical way of using this data. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. In effect, Applicants' position is that the claimed PRO317 polypeptides are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form."

Claim Rejections - 35 USC § 102

Claims 44-46, 49-51 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben (N, WO 99/09198).

Applicant argues that the effective filing date of this application is September 10, 1998 and since Ruben is dated after the effective filing date of the present application, it is not prior art under 102(a) and this rejection should be withdrawn. Applicant's

arguments have been fully considered but they are not persuasive. As discussed above, the gene amplification data disclosed in example 92 and table 8 of the present application, which was first disclosed in PCT/US98/18824, filed September 10, 1998, does not satisfy the utility requirement of 35 U.S.C. § 101 for the polypeptide. Hence, the gene amplification data does not satisfy the how to use requirement of 35 U.S.C. § 112, first paragraph, for the polypeptide. The claimed subject matter is supported by the disclosure in application serial no. PCT/US00/04414, filed February 22, 2000. Accordingly, the effective filing date claimed subject matter is February 22, 2000.

Information Disclosure Statement

Applicants request the examiner to reconsider the IDS filed 12/04/2003. Applicant's arguments have been fully considered but they are not persuasive. The information disclosure statement filed 12/04/2003 indicates, implies, or suggest that copies of the listed documents have been supplied by Applicant, when in fact they have not. 37 CFR 1.98(a) requires a legible copy of each foreign patent and each publication or that portion which caused it to be listed. Accordingly, the IDS filed 12/04/2003 will not be considered.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 16, 2004